Best Practice

STRAIGHT TO THE POINT

Chronic fatigue

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EPIDEMIOLOGY

Fatigue is common and often chronic

- Occasional mild fatigue is normal.
- Chronic debilitating fatigue that interferes with daily social and occupational function is not normal.
- The prevalence of chronic debilitating fatigue in primary care practice may be as high as 27%.[1]
- The prevalence of chronic debilitating fatigue in a population-based study was 18% (2,798/15,283).[2]

Fatigue may be disabling

- Functional impairment is comparable to that seen in patients with untreated hyperthyroidism, survivors of myocardial infarction, and survivors of sudden cardiac death.[3]

Chronic fatigue syndrome: a small subset

- About 1 of 7 patients with chronic disabling fatigue meet criteria for chronic fatigue syndrome (CFS).[1]
- CFS is defined as debilitating fatigue for 6 months without explanation after physician evaluation *plus* 4 or more of the following signs or symptoms for 6 months[4]:
  - self-reported memory or concentration impairment
  - sore throat
  - tender cervical or axillary lymph nodes
  - muscle pain, joint pain without swelling or redness
  - headaches (new or different from previous headaches)
  - unrefreshing sleep
  - postexertional malaise lasting more than 24 hours
- Currently no evidence exists that proves either a specific cause of CFS or specific pharmacologic treatment (see below).

DIAGNOSIS

Almost anything can cause fatigue

- The differential diagnosis for chronic fatigue includes virtually all advanced organ system diseases. Some leading medical causes of chronic fatigue include:

[1] *Bates DW, Schmitt W, Buchwald D, et al. Prevalence of fatigue and chronic fatigue syndrome in a primary care practice. Arch Intern Med 1993;153:2759-2765.* A prospective study conducted in a university-affiliated internal medicine practice in a teaching hospital in Boston.

[2] *Pawlikowska T, Chalser T, Hirsch SR, Wallace P, Wright DJ, Wessely SC. Population based study of fatigue and psychological distress. BMJ 1994;308:763-766.* Results of a mailed questionnaire in England.

[3] *Kroenke K, Wood DR, Mangelsdorff AD, Meier NJ, Powell JB. Chronic fatigue in primary care: prevalence, patient characteristics, and outcome. JAMA 1988;260:929-934.* Functional impairment included effects on eating, sleep, work, ambulation, recreation, and social interaction as measured by the Sickness Impact Profile.

[4] *Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. The International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994;121:953-958.*

Anemia	Drug use	Hyponatremia
Hypothyroidism	Hepatitis	Hypokalemia
Diabetes mellitus	Heart failure	Myasthenia gravis
AIDS	Sleep apnea	Addison's disease
Malignancy	Uremia	Tuberculosis

- Most of these diagnoses will be suggested by more specific symptoms, which often present well before the onset of fatigue.
- Medical evaluation fails to elicit a cause in most patients presenting with fatigue who do not already carry a diagnosis known to cause fatigue.[1]

Laboratory investigation is usually not helpful

- Most authorities recommend basic laboratory testing when patients first present with fatigue: complete blood cell count, serum electrolytes, serum creatinine, liver function tests, and thyroid-stimulating hormone (thyrotropin) level.[4] A prospective study, however, showed no significant benefit in a routine battery of laboratory tests for patients reporting fatigue for more than 30 days.[1]
- Additional laboratory testing should be directed by findings of the history and physical examination. For example, a history of injection drug use may suggest a need for serologic tests for hepatitis B or C but not necessarily an antinuclear antibody test.

Presence of occult disease

The possibility that fatigue may be an early manifestation of a serious medical illness not elicited through blood testing has been investigated by monitoring fatigued patients prospectively over time for the development of new diagnoses. At 1 year of follow-up, one study[3] showed no significant differences in new diagnoses, the incidences of diagnosed cancers, number of physician visits, or number of hospital admissions or hospital days.

This gives more weight to the conclusion that patients with chronic fatigue who otherwise have normal histories and no abnormalities on physical examination do not require extensive workups for occult medical illnesses.

Psychiatric diagnoses are common in chronic fatigue

- Patients with chronic fatigue often have undiagnosed psychiatric illnesses.[1,3]
- The prevalence of psychiatric diseases in these patients may be as high as 80%.[3]

Which came first?

- The strong association of persistent fatigue with psychiatric illness is impressive.
- This finding, more recently validated in another study,[2] prompts the question,

Table 1 *Incidence of anxiety and depression in fatigue*[3]

Symptom	Fatigued patients, no. (%) n = 102	Controls, no. (%) n = 26
Anxiety	59 (58)	3 (12)
Depression	57 (56)	0
Anxiety or depression	82 (80)	3 (12)

This was a prospective study performed on patients in a general medical practice (not a referred population). Of 1,159 consecutive patients surveyed, 220 identified fatigue as a "major" problem for more than 30 days, and 102 agreed to a full evaluation (19 were excluded because they had a major medical problem known to cause fatigue). The only laboratory test result that was significantly different between the 2 groups was the ESR ($P = 0.01$). The clinical significance of this finding is not clear.

Laboratory test values of 102 fatigued patients and 26 nonfatigued controls

Test	Patients	Controls
Hematocrit, (%)	0.42 (41.9)	0.42 (42.0)
Glucose, mmol/L (mg/dL)	6.5 (117)	5.7 (103)
Thyroxine, nmol/L (µg/dL)	113.3 (8.8)	110.7 (8.6)
Triiodothyronine, nmol/L (ng/dL)	2.2 (143)	2.1 (136)
Thyrotropin (TSH), mIU/L	2.0	1.9
Creatinine, µmol/L (mg/dL)	97 (1.1)	97 (1.1)
Potassium, mmol/L	4.5	4.4
ESR, mm/h	20.5	9.6
Chest x-ray, % abnormal	25.2	27.3

ESR = erythrocyte sedimentation rate. Values are given as SI units where appropriate, with conventional units in parentheses. Numbers represent mean values.

"Is persistent fatigue the cause or effect of depression or anxiety?" In a study of patients presenting with fatigue who were then found to have psychiatric disorders,[5] the following was noted:

- In 56% of patients, the psychiatric disorder predated the fatigue by at least 1 year.
- In 35% of patients, the fatigue and psychiatric illness began at about the same time.
- Only 10% of patients had fatigue longer than 3 months before their psychiatric illness began.

Although these findings do not prove causation, they suggest that the psychiatric disorder is a primary diagnosis and not simply a result of fatigue. This conclusion is further supported by a study demonstrating that patients with rheumatoid arthritis, a chronic and debilitating disease, have a much lower prevalence of psychiatric disease than those with chronic fatigue.[6]

[5] *Lane TJ, Manu P, Matthews DA. Depression and somatization in the chronic fatigue syndrome. Am J Med 1991;91:335-344.* Depression was measured by the Beck Depression Inventory, and anxiety was measured by the Modified Somatic Perception Questionnaire.

[6] *Katon WJ, Buchwald DS, Simon GE, Russo JE, Mease PJ. Psychiatric illness in patients with chronic fatigue and those with rheumatoid arthritis. J Gen Intern Med 1991;6:277-285.*

Etiology of chronic fatigue syndrome

- Many researchers have proposed that CFS has a specific cause that distinguishes it from chronic fatigue without the associated signs and symptoms stated above.
- Epstein-Barr virus infection, once suspected of being the etiologic agent of CFS, has been shown to be no more active in people with CFS than in those without it.[7]
- CFS is similar to chronic fatigue that does not meet CFS criteria in its high association with psychiatric disorders and the high proportion in which the psychiatric disorder predates the fatigue.[6]

[7] *Swanink CM, van der Meer JW, Vercoulen JH, Bleijenberg G, Fennis JF, Galama JM. Epstein-Barr virus (EBV) and the chronic fatigue syndrome: normal virus load in blood and normal immunologic reactivity in the EBV regression assay. Clin Infect Dis 1995;20:1390-1392.* Patients with CFS had EBV loads similar to those of nonfatigued controls.

Prognosis

- Most patients with unexplainable chronic fatigue remain fatigued on follow-up.
- In one study at 1 year of follow-up, fatigue lessened in only 29 (28%) of 102 patients.[3]
- So, although fatigue of unclear origin may not portend a serious illness, it also does not often spontaneously remit.

TREATMENT

Medications

- Many studies have assessed possible treatments, ranging from antihistamine drugs[8] to antidepressant medications[9] to vasoactive medications.
- None of these trials have shown a benefit from treatment.

[8] *Steinberg P, McNutt BE, Marshall P, et al. Double-blind placebo-controlled study of the efficacy of oral terfenadine in the treatment of chronic fatigue syndrome. J Allergy Clin Immunol 1996;97:119-126.*

[9] *Vercoulen JH, Swanink CM, Zitman FG, et al. Randomised, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome. Lancet 1996;347:858-861.* Even fatigued patients diagnosed with depression did not improve on a regimen of Prozac.

Exercise therapy

- In 1996, the Joint Working Group of the Royal Colleges of Physicians, Psychiatrists, and General Practitioners recommended graded exercise and antidepressant medication for patients with chronic fatigue syndrome.[10]
- In a trial of a graded aerobic exercise program, 66 patients with CFS who had no psychiatric disorder were randomly allocated to aerobic exercise (treatment) versus flexibility exercises (control).[11] After 12 weeks, 17 of the 33 treated patients (51%) felt significantly improved compared with 9 (27%) of the 33 controls. The total fatigue score was significantly better in the treatment group.

[10] *Joint Working Group of the Royal Colleges of Physicians, Psychiatrists and General Practitioners. Chronic Fatigue Syndrome. Council Report CR54. London: Royal College of Physicians; 1996.*

[11] *Fulcher KY, White PD. Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. BMJ 1997;314:1647-1652.*

- In a more recent trial, 136 patients with CFS were randomly assigned to graded exercise 3 to 5 times per week, fluoxetine hydrochloride (20 mg a day), both, or neither.[12] At 6 months, patients randomly assigned to exercise had modestly improved work capacity and less fatigue, but patients randomly assigned to take fluoxetine showed no improvement in these variables.

[12] *Wearden AJ, Morriss RK, Mullis R, et al. Randomised, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome. Br J Psychiatry 1998;172:485-490.*

Cognitive therapy

- The most impressive increases in functional status reported in studies of fatigued patients have occurred with cognitive behavioral therapy, an approach based on the theory that "inaccurate and unhelpful beliefs, ineffective coping behavior, negative mood states, social problems, and pathophysiological processes all interact to perpetuate the illness."[13]
- According to theory, a person's belief that he or she will fail in a certain activity may lead to a loss of energy in initiating that activity. Similarly, a belief that CFS is necessarily debilitating may lead to a decreased effort to try to overcome it, thereby perpetuating the fatigue.
- Sixty patients consecutively referred to an infectious disease clinic who met the CFS definition by the Oxford criteria[14] were randomly allocated to standard medical care or cognitive behavior therapy plus standard medical care.[13] The results were as follows:

[13] *Sharpe M, Hawton K, Simkin S, et al. Cognitive behaviour therapy for the chronic fatigue syndrome: a randomised controlled trial. BMJ 1996;312:22-26.* Results were sustained for 1 year after therapy was discontinued. Cognitive therapy also increased the proportion of patients who improved in their work status (63% vs 20%).

The following are the main concerns about putting this study into practice:

- Therapy was administered by psychiatrists or psychologists.
- Therapy consisted of 16 one-hour sessions over 4 months.
- Patients were selected from a subspecialty referral center.

[14] *Sharpe MC, Archard LC, Banatvala JE, et al. A report: chronic fatigue syndrome: guidelines for research. J R Soc Med 1991;84:118-121.* This definition is notable for including the presence of mental fatigue ("A subjective sensation characterized by lack of motivation and of alertness").

Table 2 *Cognitive therapy in the treatment of CFS (N = 60)*

Results	Cognitive therapy, no. (%)	Standard care, no. (%)	ARR, %
Achieved normal function	22 (73)	8 (27)	47
Significantly improved function	22 (73)	7 (23)	50

ARR = absolute risk reduction (for every 100 patients treated, 47 achieved normal function)

Additional findings

- Patients receiving cognitive behavioral therapy were far less likely to report that they were avoiding exercise.
- Patients receiving cognitive therapy were also less convinced that their illness was mainly physical or that it was caused by a virus.
- This study was reinforced by the results of another trial of 60 patients that demonstrated similar outcomes.[15]

[15] *Deale A, Chalder T, Marks I, Wessely S. Cognitive behavior therapy for chronic fatigue syndrome: a randomized controlled trial. Am J Psychiatry 1997;154:408-414.* At final follow-up, 19 (70%) of the 30 patients in the cognitive behavior therapy group achieved good outcomes (substantial improvement in physical functioning) compared with 5 (19%) of the 30 in the relaxation group.

Cognitive therapy: study conclusions

- Patients' beliefs about their illnesses affect their outcome. Avoidance of exercise and emphasis on the physical nature of the illness and its possible viral cause are associated with a worse prognosis.
- A collaborative approach with the patient, emphasizing reevaluating illness beliefs and behavior, may lead to substantial improvement in function.
- Patients with unexplained chronic fatigue should be considered for referral for cognitive behavior therapy.

SUMMARY OF PRINCIPLES IN MANAGEMENT OF CHRONIC FATIGUE

- Fatigue is a common and often serious problem.
- The differential diagnosis is long and does not lend itself to a universal approach.
- Comprehensive laboratory investigation is usually not helpful.
- Patients with CFS represent a small subset of all patients with fatigue.
- There is no evidence to suggest that patients with CFS should be treated differently from other patients with fatigue.
- Medical therapy is of little or no benefit in the treatment of chronic fatigue.
- Cognitive behavioral therapy has been shown to substantially decrease symptoms and improve function in patients with chronic fatigue.
- Graded exercise has been shown to produce modest improvement in patients' work capacity and fatigue.

Salmon River, day 8

It was water that carried us, playful and laughing
down steepening canyons of granite, basalt
over Volkswagen boulders, down
to warm benches all cobbled
or to beaches smooth as dunes.

It was water we carried, five-gallon jerrycans
for washing and cooking and mixing our drinks
and water that bathed us in sulfurous hot springs
and water sounds filling our ears every night,
saltwater that dripped down our cheeks
after talk turned to childhood, and before turning in
under star fields unnamable, we voided
our water back into the stream.

But after the takeout, near Shoup
it was glacier-melt water, deceptively playful
that carried that peel-bark stob Ponderosa
and stuck it cross-current
in the ill-chosen path of the Sunday-fun boater
where 85 bystanders, helmeted kayakers,
poker-faced deputy, off-duty nurse,
ambulance, fire-rigs and
all our good wishes
trickled to nothing
like tears through the fingers
of the bank-stranded girlfriend
and disappeared into the dry desert sand.

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I shall be your Vasari

I was in your club the other day, Guilliamo,
for the Art League show.
Staid brownstone, its somber rooms
recalled to mind our short acquaintance.
My career as doctor was just beginning,
yours as artist coming to an unexpected end.

Your brother had volunteered for Vietnam.
He was furious with you,
not fighting for your country.
Malingerer he had called you,
with your recurrent bouts of pain.
But that was before we found the cancer.
Now there was only time enough to wait.

I thought of this through the year of your illness,
as we sat in the Salmagundi,
talking art and politics over dinner
and as I watched you paint our protests,
the crowds in gray and black tones,
marching up the canvas to Bryant Park.

Once again in Bellevue, your bowel obstructed,
who jabbed you with needles, forced you
to swallow long rubber tubes?
It was I who had become more than your doctor.
We both knew all help was transitory.

You had entered that fierce land
in which there was no cure.
I could not be your Orpheus,
but now as your Vasari,
I shall tell of your short life.
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